Just one very brief question, and then I'll let you move on.

Was there an internal examination on the females or just external?

DR. PARISI: My understanding is that, for the females, particularly those who had the concerns about the clitoromegaly and the labial scrotal fusion or the other?

DR. JOHNSON: All infants.

DR. PARISI: I do not believe there was an internal examination. That was not the standard of the physical exam.

DR. JOHNSON: Thank you.

DR. VISCARDI: Thank you. I am an neonatologist, so some of my questions are going to focus on the neonatal outcomes.

I guess my first comment is, as I looked at the table that was provided to us on outcomes, all of the morbidities were fairly low.

And then I realized that, yes, these are -- many of these are babies who are born greater than 32 weeks, but I also wondered if the incidences

that are given -- for instance, like for intra-ventricular hemorrhage, to diagnose that, you have to have done a cranial ultrasound.

And was this just recorded if they had an ultrasound done, or was that part of the protocol?

And how many ultrasounds did each of the babies have?

Because, again, you're only going to ascertain whether they had that outcome if you did more than one ultrasound.

The other cranial ultrasound outcome that would have been of considerable interest is peri-ventricular luekomalacia and that was not reported.

So I was just curious as to whether that just was not found in any of the infants or whether that wasn't looked for or recorded?

And the other incidence that was reported to be different was the patent ductus arteriosus.

And, again, depending on the unit, they may diagnose that either as a clinically significant PDA on clinical findings, whereas other units might make

that diagnosis by screening all infants of a particular size by doing a cardiac echocardiogram.

So, again, I wasn't sure if there was specific criteria for which some of these diagnoses were made?

DR. HICKOK: Yes. Let me review with you just briefly the findings on this.

And, again, in the study, because these were not primary endpoints of the study that were looked at, there was not a pre-specified, for example, you know, an intra-cranial ultrasound shall be done on all infants and shall be done every two to three days, or things like that.

So we do know that the physicians managing these patients actually manage them clinically as they would, and there was not, you know, pre-specified tests that would be ordered at a regular interval like this, and that the intra-ventricular hemorrhage was a diagnosis by ultrasound.

Your second question, I think, unless you have another comment about that, relates to PDAs?

DR. VISCARDI: Well, I guess this would actually go towards both of those, in that the incidences are then given for the total sample when and what should have happened is the incident should have been given for those who actually had a scan done.

And I don't know if that was different between the two samples.

So could the difference that you're seeing just be because you did more scans in one sample than the other?

Because the other thing I can tell you is in most units they're not going to do ultrasounds routinely in babies over 32 weeks unless there is some clinical reason to suspect an intra-cranial problem, like seizures or an enlarged head, or, you know, some clinical indication. But they're not going to screen all those children.

And some units have a very specific criteria for which they -- you know, they do one in the first week, and a month of age, and prior to discharge, and may do several in between.

And the number of scans matter as to whether

you'll make that diagnosis or not.

DR. HICKOK: Again, I believe that the study was done, and these findings recorded, based on clinical examination, with the assumption that the most severe intra cranial hemorrhages, at Grade 3s and Grade 4s, that the majority of those would probably be detected because of suspicion from, you know, the clinical findings of the baby.

But we do not have, you know, pure incidence rates, as you have pointed out.

DR. VISCARDI: I guess the other thing to point out, was you reported the total incidence of IVH, but, in fact, since severity is Graded from 1 to 4 with 1 and 2 being considered more mild and maybe having less impact on the child's later development; but, as you point out, Grade 3 and 4 being more severe, there was no Grade 3 and 4 in the placebo group. The only Grade 3 and 4s were reported in the treatment group.

DR. HICKOK: Yes. And --

DR. VISCARDI: And the only reduction in IVH was in Grade 1 and 2.

DR. HICKOK: Yes. And the data that you're referring to, again, when we broke these -- I'm sorry, when we broke these out by Grade 3 versus Grade 4, there were, you know, two cases in the 17-p group, Grade 3 or 4 versus none in the placebo group.

And other rates of intra-cranial hemorrhage; again, 0.3 percent versus, I'm sorry, I can't see, thank you, versus 1.3 percent.

But, again, there's a lot of variability in these numbers because, as you pointed out, they're low-level incidence rates.

And the study, itself, was looking primarily at pre-term birth prevention and prolongation of pregnancy.

These neonatal outcomes are certainly of importance, but it would have been a much more complicated study had there been a lot of pre-specified examinations done on children during that time period.

You also asked me a question about patent ductus arteriosus, and I would be pleased to --

DR. VISCARDI: I guess my question was, was that diagnosis made if it was a clinically diagnosed PDA, or was it on the basis of a cardiac echocardiogram, which gets back to the same point that -- with the IVH; that if it's based on a screening test, then the denominator should be the number of children who were screened?

DR. HICKOK: Yes. I'd like to actually ask Dr. Michael O'Shea, a neonatologist, at Wake Forest University, and ask him, at Wake Forest, at the time that this was done what general diagnostic criteria were used, Dr. O'Shea, at that point?

Again, recall that Wake Forest was one of the 17-p study centers.

DR. O'SHEA: Mike O' Shea from Wake Forest.

I think Dr. Viscardi's point is well taken. There probably is an ascertainment bias, in that, at Wake Forest, and I suspect many center, cardiac echos are done not on a screening basis but rather if symptoms develop, then later dependency.

I think the same is also true for the ascertainment of intra-ventricular hemorrhage.

However, necrotizing enterocolitis, I would suspect to be less subject to ascertainment bias, and certainly days on the ventilator would be, I think, very unlikely to be very affected by ascertainment bias.

DR. HICKOK: All right. Thank you.

And I certainly don't want to ignore Dr. Davidson and his question about the heart abnormalities.

I would be pleased to turn back to that, if you would like me to, Dr. Davidson?

(Pause.)

DR. HICKOK: In terms of the cardiac findings, as we stated before, there is a low rate of cardiac abnormalities that were observed at birth, in both in the 17-p and the placebo groups.

And these rates were 0.5 percent in the 17-p versus 0.5 percent in the placebo.

And going back to the previous question, just about the incidence of about patent ductus arteriosus, again, it was slightly higher in the placebo group.

At the time of the follow-up study examination, as I mentioned before, there were a number of infants in the 17-p group that had the check box, you know, indicating that there were areas in the heart examination.

And, specifically, 4.6 percent of the infants in the 17-p group had a heart murmur and 0.5 percent were recorded as having an irregular rhythm.

What NICHD did at that time is to go and look at other parts of the follow-up examination in terms of functional capabilities, and things like that.

And then, also, to go back to the initial birth hospitalization and look for, you know, problems that occurred during that period of time.

And it was determined, again by NICHD, that all of these children that had murmurs noted in the infant follow-up study did not have any indication of ongoing functional disorders, and in one case had a cardiac -- one of the cases there was a cardiac anomaly noted at birth with no further follow-up.

One of the cases there was a patent ductus arteriosus.

And, again, I would just like to remind people, as Dr. Parisi pointed out, that the heart is essentially formed by the time 17-p is administered at this point in pregnancy. Nonetheless, these are good questions.

DR. GILLEN: Yes. You noted earlier that, based upon the results of a formal in-term analysis, that DSMC had recommended termination on this study early.

I was wondering if you could specify the stopping rule that was used in the protocol, and also how many previous interim analyses had taken place, if any? And what points, in terms of numbers of patients enrolled, those had taken place?

DR. HICKOK: Yes, thank you.

And I'd like to invite our bio-statistician, Dr. Anita Das, up here to respond to that.

DR. DAS: Anita Das, representing Adeza.

The Data Safety and Monitoring Committee interim analysis, use a land of mats procedure with an O'Brien Fleming (ph) boundary.

And there were two previous analyses conducted.

The first time when 15.2 percent of the patients had been enrolled, and then the second time when approximately 70.2 percent of the patients had actually not been enrolled but completed follow up.

And at the second meeting, the efficacy had crossed the bounds, and the boundary was 0.015, and that's when the DSMC stopped the study.

And, at that time, 463 patients had been enrolled.

DR. GILLEN: And the results that we are seeing, are they adjusted at all in terms of the point estimates or, inference that we're seeing, adjusted for the interim analyses that took place?

DR. DAS: Yes. The primary outcome of pre-term delivery less than 37 weeks is adjusted for the two interim analyses.

The final alpha level is 0.035.

DR. GILLEN: Okay. Thank you.

DR. DAVIDSON: Dr. Steers.

DR. STEERS: Yes.

While it is recognized that 17-p was administered probably after genital development was

complete, my theoretical concern is, given this drug has been around since the 1950s, is there any available data at the time of puberty or after puberty, sexual function, fertility and reproductive function in children, who had been exposed in utero to this drug, especially germane with the congenital hyperplasia concerns that have been raised in adulthood and the long-term effects?

Is there -- they had any either animal data with reproductive function or human data that anyone's aware of?

DR. HICKOK: We're not aware of animal data on 17-hpc and reproductive function.

There is some information that I will present to you here that may be pertinent.

Dr. Charney, would you like to describe -- or Dr. Singh?

Dr. Pamela Singh, whose interest is in preclinical studies and toxicology, and she will describe the findings from this one study that is pertinent, I believe, to your question.

DR. SINGH: Pamela Singh, representing Adeza.

Excuse me, first, I'd like to request a different slide.

DR. HENDERSON: I'm sorry?

DR. SINGH: That's all right. I'll ask A/V to help me out with a different slide.

(Pause.)

DR. SINGH: And, specifically, I'm only going to speak to the point of the animal studies, and then, perhaps, I can pass this question on to Dr. Melissa Parisi.

Okay. So the question really was, are there any animal studies that indicate any issues with congenital anomalies.

And, yes, in fact, there were animal studies; however, these were negative.

And I'd like to point you to the slide that will be up shortly.

Okay. So in the rodent model for reproductive toxicity, teratogenicity was evaluated in mice. And, as you can see, in the C-57 block, six mice, there was no teratogenicity or maternal toxicity up to 10 times the clinical dose.

And then, also, in Swiss Webster mice, a different strain, teratogenicity was tested up to approximately 200 times the clinical dose. This, in fact, by a subcutaneous route.

However, at that extreme amount of exposure you would imagine that the systemic exposure was certainly well beyond the clinical.

So, again, you see two negative studies in terms of teratogenicity in mice, with 17-hpc the active.

Now, I'd like for you to look at the non-human primate data.

You'll notice this slide has shifted upwards. I actually -- the title of the slide is "17-hpc Teratogenicity Data in Rhesus and Cynomolgus Monkeys."

So there are actually two different species of monkeys here. You just can't see it because it's above the line on the screen there.

But the important part of this slide is just that studies were conducted in both Rhesus and Cynomolgus monkeys to evaluate teratogenicity in

17-hpc, and no teratogenicity was found.

And I'll point out that, in this study, treatment -- exposure actually occurred earlier than clinically indicated.

It was during the first third of gestation when treatment was initiated; whereas, in the clinic, exposure is not initiated during the first trimester. That is one point to consider.

And then I also want to just point out that this is an intramuscular injection just like the clinical round of exposure.

DR. STEERS: My question isn't directed at teratogenicity; more as, did they let the primates grow through adolescence and adulthood and look at reproductive potential or sexual functioning in these animals? That's the point I'd like to make.

DR. SINGH: Okay. So those two sets of studies in rodents and non-rodents, did not look at an evaluation of sexual functioning, as you say.

They were just under fairly standard teratogenic evaluation, which, as animals go through the Caesarian -- there is the Caesarian section and

then there is an evaluation, of the fetuses at that point.

However, there are other studies that I don't actually have a slide prepared for but that did evaluate an F-1 generation in mice.

And there are some data that suggests that there may be interference with male spermatogenesis. But, to my knowledge, that is the only interference that I've seen on a non-clinical.

DR. HICKOK: Dr. Steers, would it help you if we looked more on molecular level to, you know, how 17-p is metabolized, and androgenic or estrogenic properties? Would that be of assistance to you?

DR. STEERS: Well, it is not so much the acute effects, but, obviously, if this is a chronic exposure in uteral to receptor development, et cetera, that you might not see expression until during puberty or later of things like genital growth, things like sexual orientation, things like sexual functioning.

So it would almost be in case reports of anything long-term, or even like fertility, on what

would happen with spermatogenesis in particular, if these levels are raised, and what would happen long term.

DR. HICKOK: Yes. I would like to remark that there is, you know, the ADR and AERS database that are available; again -- you know, going back some 30 years, that can be voluntarily brought up, you know, in response to questions about Delalutin because it was approved in 1955.

We have reviewed those data and found really no consistent patterns of things like that that were noted.

Of course, there is not good denominator data for that, but the AERS/ADR database does provide a way at identifying safety concerns.

DR. STEERS: Do we have access to that database from the Delalutin data as long-term?

DR. HICKOK: I'm sorry, I didn't --

DR. STEERS: Do we have access to that database for safe, long-term follow-up from the Delalutin?

DR. HICKOK: There is -- there are database -- the AERS and ADR databases, specifically, for

Delalutin, yes. And we have reviewed those.

DR. DAVIDSON: Dr. Carson.

DR. CARSON: I have several related questions, so let me just ask them and then you can discuss this.

They all are based on the fact that I noticed the impressive wide-range of body mass index in your patients in the study, from a BMI of 15 to 72.

And it made me wonder how you came up with the dose to treat all these patients at the same dose, and whether you compared efficacy in groups of obese, overweight, et cetera, in groups of body mass index?

And, then, finally, what kind of serum concentrations you had in all of these patients?

DR. HICKOK: Let me answer your questions separately here if I can.

The NICHD 17-p study, again, was not a variable dose study. It was to replicate that some of these very promising findings that had been identified before, so there was not consideration given to, you know, looking at variable different doses.

The 250 mgs per week that was administered, you know, again from 16 through 37 weeks of gestation or delivery, was noted to be effective in a number of these other studies, so there wasn't any notion at the time of varying that dose.

And, in fact, the degree of efficacy was so great one might even argue that, you know, why try it when you've got 34 percent reduction in pre-term birth, over all, you know, should you look beyond that.

The second part of your question, I believe, related to serum studies.

Serum studies were not part of the evaluation of the NICHD study. We do have some PK studies that we would -- and serum studies that we would be pleased to present to you, if that would be of help?

DR. CARSON: I would like to see that. Do you have it with you?

DR. HICKOK: Yes. Yes.

DR. CARSON: Oh, great.

DR. HICKOK: I'm going to invite Dr. Martha Charney up, who is going to describe about what is

known about pharmacokinetics.

DR. CARSON: And this is in pregnant women?

DR. HICKOK: This is not in pregnant women. This is in a sample of women, as she'll describe to you, that were not pregnant at the time.

DR. CHARNEY: Martha Charney, representing Adeza.

There was one published study, which was all we could find in the literature, on the pharmacokinetics of 17-hpc.

This shows the single -- the plasma concentrations after a single dose of 1,000 mgs of 17-hpc to subjects who had endometrial carcinoma.

Next slide, please, 437.

From that data -- these are the pharmacokinetic parameters, and you can see that the T-Max occurred quite late. That's 4.6 days after injection.

The C-Max was about 30 nanograms per milliliter at this high dose. The half life was 7.8 days.

And it is my opinion, based on the long T-half and the long T-Max, that the driving force in the pharmacokinetics of 17-hpc is actually the

release of the drug from the intramuscular depot.

And, given that, I think that would be independent of whether or not it was a pregnant woman or a non-pregnant woman.

There is additional data that came from the same source.

These were, again, patients with endometrial carcinoma who received an initial 5 doses, 1 per day, followed by either once weekly or twice weekly, and continued administration of the 1000 mgs.

And you can see that it does tend to level out and provide a long-term plateau of concentration on that.

DR. CARSON: So, do you -- I'm sorry, I just don't know the nanomole conversion to --

DR. CHARNEY: Oh, yeah. That's a little confusing because they reported it in nanomoles -- or in micro moles -- nanomoles, and the FDA, for its submission, we converted it all to nanograms per milliliter.

But on the single dose study, it was -- C-Max was approximately 60 nanomoles, which

converted over to about 30 nanograms per milliliter.

So the other with the multiple dose, which was around 200 nanomoles per liter, would -- I think we -- that would be about four times.

We're talking probably 100 nanograms per milliliter or less.

DR. CARSON: But you're using a quarter of the dose.

DR. CHARNEY: And we're using quarter of a dose. So, yes.

DR. CARSON: So you're probably raising the pregnancy concentration by about 3 percent?

DR. CHARNEY: Oh, if you're talking about --

DR. CARSON: With, with 200, you have your baseline 17-hydroxyprogesterone in pregnancy, and, by giving 250 mgs, you're raising the concentration by maybe 3 percent? Is that right?

DR. CHARNEY: Actually, this is the hydroxyprogesterone caproate. It does not metabolize to either hydroxyprogesterone or progesterone. It has a totally different metabolic pathway, and I think our chemistry expert, if you

want, can speak to that.

DR. CARSON: Yes. So you're measuring the hpc rather than just the --

DR. CHARNEY: Yes.

DR. CARSON: Gotcha.

DR. DAVIDSON: Okay. I know we have a number of other Committee members who have questions. I have a list of half dozen. We will probably give you priority later.

I want to thank Dr. Hickok for giving us this bonus question and answer period.

(Applause.)

I think we needed it.

And let's take a 15-minute break and reassemble at 10:45.

(Recess.)

DR. DAVIDSON: We have a large agenda, and it is really important that we stay on schedule.

We next have the presentation for the Agency, and this will be led with Dr. Wesley.

DR. WESLEY: I'll give you a few minutes to get to your seats.

(Pause.)

Advisory Committee members, representatives from Adeza Biomedical, representatives from the FDA, and guests, I am Barbara Wesley, and I am the primary medical reviewer for this new drug application, or NDA.

In my presentation, I plan to review, again, the clinical program of NDA 21-945, provide you with the FDA analyses of the data submitted, and summarize the issues for you to consider.

The proposed indication for 17 alpha hydroxyprogesterone caproate, which I will also call 17 hydroxyprogesterone, proposed name Gestiva, is a prevention of pre-term birth in pregnant women with a history of at least one spontaneous pre-term birth.

Gestiva is to be administered in the intramuscular route at a dose of 250 mgs once a week, beginning between 16 weeks, zero days and 20 weeks, 6-days gestation, until week 37, or birth, whichever occurs first.

An overview of the clinical studies will be

presented in the next slide.

This application included data from three studies conducted by the National Institute of Child Health and Development, Maternal Fetal Medicine Network Units.

The initial formulation study, 17-pIF, was a randomized vehicle-controlled study with a target enrollment of 500 subjects, but only 150 subjects were enrolled and treated.

It was terminated prematurely due to a recall of the study drug.

The principal efficacy and safety study, 17pCT-002, had the same design as the initial formulation study.

It also was to enroll 500 subjects; however, because the boundary for the test of significance for the efficacy threshold was crossed before enrollment was completed, enrollment in the trial was stopped prematurely.

A total of 463 subjects were enrolled in this study; 310 in the 17-hydroxyprogesterone arm, and 150 in the vehicle arm.

At the request of the FDA, another study, 17-p follow-up, was conducted.

Children whose mothers participated in the principal safety and efficacy were evaluated for long-term health and developmental milestones.

278 children, from 30 to 64 months of age, were enrolled; 194 from the 17-hydroxyprogesterone arm, and 84 from the vehicle arm.

An overview of the principal study is shown in the next slide.

The principal study was a double-blind, vehicle controlled trial that randomized subjects 2-to-1 to 17 alpha hydroxyprogesterone caproate or vehicle.

Inclusion criteria were pregnant women with a history of a previous spontaneous, singleton, pre-term birth, who were at a gestational age between 16 weeks, zero days, and 20 weeks, 6 days at randomization.

The main inclusion criteria included a known major anomaly.

I want to make sure I said "exclusion criteria."

Included a main -- a known major anomaly, prior progesterone or heparin treatment in a current pregnancy, a history of thrombo embolic disease and maternal medical obstetrical complications, including a current or planned cerclage, hypertension requiring medication, or a seizure disorder.

Studied medications were 17 alpha hydroxyprogesterone caproate, 250 mgs per milliliter, in castor oil, benzyl benzoate, and benzyl alcohol, or vehicle, which also consisted of castor oil, benzyl benzoate, and benzyl alcohol, but without the progesterone.

The dosing regimen was 250 mgs, weekly injection of 17-hydroxyprogesterone or vehicle through week 36, 6 days, or delivery, whichever occurred first.

The primary efficacy endpoint was percent births less than 37 weeks gestation.

Additional endpoints requested by the FDA included percent births less than 35 weeks and less than 32 weeks gestation, and a composite index of

neonatal morbidity.

The composite was based on the number of infants who experienced any one of the following: death, respiratory distress syndrome, bronchial pulmonary dysplasia, Grade 3 or 4 intra-ventricular hemorrhage, proven sepsis, or necrotizing enterocolitis.

This study was designed to enroll 500 subjects.

However, as mentioned previously, because the boundary for the test of significance for the efficacy threshold was crossed before enrollment was completed, only 463 subjects were randomized and treated with studied medication; 310 in the 17-hydroxyprogesterone arm and 153 in the vehicle arm.

The disposition of these subjects was as follows:

279 subjects completed the study in the 17-hydroxyprogesterone arm versus 139 in the vehicle arm;

27 subjects withdrew from treatment in the 17-hydroxyprogesterone arm versus 14 in the vehicle arm, but remained in the study.

In the 17-hydroxyprogesterone arm, 6 withdrew due to an adverse event compared to 3 in the vehicle arm; 4 subjects were lost to follow-up, all in the 17-hydroxyprogesterone arm.

The primary efficacy endpoint was percent of pre-term births less than 37 weeks gestation.

The primary efficacy analysis was based on the intent to treat ITT population all subjects who received studied medication.

Of the 310 subjects treated with 17-hydroxyprogesterone, 115 or 37.1 percent, delivered prematurely.

Of the 153 subjects treated with vehicle, 84 or 54.9 percent delivered prematurely.

There was a 17.8 percent reduction in pre-term birth below 37 weeks.

The 95 percent confidence interval for the reduction in pre-term births ranged from minus 28 percent to minus 7 percent.

It is noteworthy that the pre-term birth rate of 54.9 percent in the vehicle arm was considerably greater than the background rate of 36 percent that

was used to power this study.

The rate of 54.9 percent pre-term births is also considerably higher than that of the control arm; 36 percent in another Maternal Fetal Medicine Network study, the Home Activity Uterine Monitoring study.

Finally, I bring to your attention that the pre-term birth rate of 37.1 percent in the 17-hydroxyprogesterone arm is no lower than the pre-term birthrate of 36 percent in the control arm of the Home Activity Uterine Monitoring study.

We were particularly interested in the pre-term birth rate at gestational ages less than 37 weeks since births at these lower gestational ages are a more accurate predictor of infant mortality or morbidity.

This slide lists the percentages of pre-term birth at selected gestational ages less than 37 weeks.

The analysis present on this slide is slightly different from that provided in our background package.

In the previous analysis, no data from the four subjects who were lost to follow-up were included, and these subjects were considered as treatment failures at all time points.

In the analysis presented in this slide, all available data from these subjects were included.

In this analysis requested by the FDA statistician, confidence intervals were adjusted for the two interim analyses and the final analysis, using a "P" value boundary of .035 to preserve the overall Type 1 error rate of .05.

The percentages of pre-term births in the 17-hydroxyprogesterone arm, at less than 35 and less than 32 weeks were numerically lower than those in the vehicle arm.

The point estimates of the differences were negative 9.4 percent and negative 7.7 percent, lower than in the vehicle arm at less than 35 and less than 32 weeks, respectively.

However, based on the adjusted 95 percent confidence intervals, the upper limits suggest that 17-hydroxyprogesterone may be no better than

vehicle.

In the previous slide, the percent differences in pre-term birth at specific gestational ages, were shown.

In this slide, the proportion of subjects continuing to be pregnant at each week after enrollment is shown.

The vertical line marks 37 weeks gestation, the primary endpoint.

Not shown on the previous slides is that a lesser proportion of subjects in the 17-hydroxyprogesterone arm continued to be pregnant compared to the vehicle arm, up to 24 to 25 weeks gestation.

Beginning at about 27 weeks gestation, a greater proportion of subjects remain pregnant in the 17-hydroxy-progesterone arm, at each week of gestational age.

The early increase in fetal loss in the 17-hydroxyprogesterone arm is of concern. I will further discuss this finding later in my presentation.

Another way to look at the potential efficacy of 17-hydroxyprogesterone treatment is to compare the mean gestational ages between both arms.

The mean gestational age in a 17-hydroxyprogesterone arm was one week greater than the vehicle arm; 36.2 weeks in the 17-hydroxy-progesterone arm versus 35.2 weeks in the vehicle arm.

Consistent with the finding of a higher gestational age in the 17-hydroxyprogesterone arm, the mean birth weight was also 178 grams higher in this arm. However, this difference was not statistically significant.

Another way to assess the effectiveness of treatment is to determine the percentage of birth below 2,500 grams and below 1,500 grams, which is also consistent with 32 weeks gestation.

The percentage of infants less than 2,500 grams was 13.8 percent lower in the 17-hydroxyprogesterone arm.

For infants less than 1,500 grams, the percentage was 5.3 percent lower in the 17-

hydroxyprogesterone arm.

However, based on the 95 percent confidence interval, the percentage of infants less than 1,500 grams in the 17-hydroxyprogesterone arm was not statistically significant.

Reduction of neonatal deaths, without an increase in fetal wastage, is the ultimate goal in preventing pre-term birth.

This slide describes all deaths in the principal study.

There was an observed increase in second trimester miscarriages; 5 in the 17-hydroxyprogesterone arm versus none in the vehicle arm.

In contrast, there was an observed reduction in neonatal deaths in the 17-hydroxyprogesterone arm -- 2.6 percent versus 5.9 percent in the vehicle arm.

However, the observed reduction in neonatal deaths was offset by an increase in second trimester miscarriages and stillbirths; thus, when considering the overall mortality, there was no net survival benefit.

This graph illustrates the proportion of fetal or neonatal deaths from the onset of treatment.

On the "X" axis, you see days from the onset of treatments to fetal or neonatal death.

On the "Y" axis, you see the proportion of fetuses or neonates who are surviving.

The red line represents the 17-hydroxyprogesterone arm, the blue line represents the vehicle arm.

I want to bring to your attention once again, that there is a lower proportion survivors in the 17-hydroxyprogesterone arm until about 75 days after the onset of treatment.

Thereafter, the proportion of survivors in the 17-hydroxyprogesterone arm remain slightly above that in the vehicle arm.

To gain additional insight into the significance of the findings of early fetal losses, we reviewed the literature.

Data in a 1990 review by Keirce described four studies where treatment with 17-alpha-hydroxyprogesterone caproate was begun early in

pregnancy, and data on miscarriages were provided.

Two of the trials, the Johnson and Yemeni trials, showed a numerically greater proportion of miscarriages in the 17-hydroxyprogesterone arm.

The other two trials, those by LaVine and Sherman, did not. The LaVine trial reported more miscarriages in the vehicle arm.

In addition to reduction of mortality, reduction of neonatal morbidity is a goal of therapy to prevent pre-term birth.

Major neonatal morbidities are listed on this slide.

We have chosen not to provide "P" values for the differences for several reasons.

These comparisons were post-hoc analyses. Event rates were low, and no adjustments were made for the multiple endpoints.

However, there are some noteworthy observations.

There was a decrease in the percent of respiratory distress syndrome, broncho-pulmonary dysplasia, and necrotizing enterocolitis in the 17-

hydroxyprogesterone arm.

However, there was also a small increase in the percent of Grade 3 and 4 intra-ventricular hemorrhage and proven sepsis in the 17-hydroxyprogesterone arm.

The individual morbidities listed in this slide were grouped to form a composite index of morbidity.

All infants with one or more of the listed morbidities were counted in the index.

A lower percent age of infants in the 17-hydroxyprogesterone arm, 11.9 percent, compared to the 17.2 percent in the vehicle arm, had one or more of the morbidities that comprise the composite index.

However, the difference between the treatment arms was not statistically significant.

I will now turn your attention to maternal safety findings.

Adverse event data were not collected in the usual manner for data submitted to the FDA.

Rather than collecting all adverse events, subjects were asked if they had any symptoms or

complaints that they thought were related to the study medication.

There were no maternal deaths.

There were three reports of a serious adverse event, all in the 17-hydroxyprogesterone arm. None were thought to be, by the investigators, to be related to the study drug.

The serious adverse events were a pulmonary-embolus eight days after delivery, a case of cellulitis at the study medication site, and a patient with postpartum hemorrhage, respiratory distress, and endometritis.

Eleven (11) subjects discontinued because of an adverse event;

Seven (7) subjects were in the 17-hydroxyprogesterone arm; 3 with urticaria, 2 with injection site pain or swelling, 1 with arthralgia, and 1 with weight gain.

Four (4) subjects were in the vehicle arm, two with pruritus, one with urticaria, and with injection site pain.

Common adverse events will be described in the

next slide.

The majority of all adverse events were related to injection site reactions.

Injection site pain was the most commonly reported adverse event affecting a third of subjects in each arm.

Injection site swelling was the next most common adverse event, followed by urticaria, pruritus, and injection site pruritus.

We identified three out of nine complications of pregnancy reported by the applicant where the percentage of effected subjects was proportionately greater in the 17-hydroxyprogesterone arm.

The pregnancy complications were: Gestational diabetes, oligohydramnios, and preeclampsia.

The numbers of subjects with these complications in both the principle study, CT-002, and the initial formulation study, IF-001, that was terminated prematurely due to a recall of the study drug, are listed on this slide.

There was a small increase in the percentage of subjects with gestational diabetes in the 17-

hydroxyprogesterone arm in the principal study.

In the initial formulation study, there were eight cases of gestational diabetes in the 17-hydroxyprogesterone arm compared to no cases in the vehicle arm.

This difference approached statistical significance.

In terms of oligohydramnios, there was almost a three-fold increase in the percentage of subjects with oligohydramnios in the 17-hydroxyprogesterone arm of the principal study.

The percentage of subjects with pre-eclampsia in the 17-hydroxyprogesterone arm in the principal study was almost twice that in the vehicle arm.

The percentage of subjects with pre-eclampsia in the 17-hydroxyprogesterone arm in the initial formulation study was also higher.

Although the initial formulation study was terminated prematurely, I will briefly describe some of the findings from this study.

The design of this study was identical to that of the principal efficacy and safety study;

namely, double-blind, vehicle controlled, and randomized 2-to-1, 17-alpha- hydroxyprogesterone caproate to vehicle.

This study was terminated prematurely because of a recall of the study drug.

150 subjects were randomized prior to the recall; 104 subjects either completed treatment or withdrew for reasons other than recall of the study drug.

Of these 104 subjects, 65 subjects were in the 17-hydroxyprogesterone arm, and 39 subjects were in the vehicle arm.

Key findings from this study are presented in the next slide.

The top of this slide shows the proportion of subjects who delivered at less than 37 weeks gestation, among those subjects not affected by the study drug recall.

These are the subjects who either completed treatment or terminated for reasons unrelated to the recall.

The percentage of pre-term births in the 17-

hydroxyprogesterone arm was slightly higher than that in the vehicle arm, 43.1 percent versus 38.5 percent.

The lower portion of the slide lists all fetal and neonatal deaths from all enrolled and treated subjects.

The increased miscarriage or stillbirth rate that was observed in the principal study was not seen in this study.

There was only one case of miscarriage in each treatment arm.

In terms of stillbirths, there were two cases in the vehicle arm compared to one case in the 17-hydroxyprogesterone arm.

There were two neonatal deaths in the 17-hydroxyprogesterone arm, and none in the vehicle arm.

The next slide provides an overview of the follow-up study of children born in the principal study.

The objective of this study was to evaluate the long-term health and development of children who

were born in the principal study.

Only 14 of the original 19 sites were remaining in the Maternal Fetal Medicine Network at the time this follow-up study was conducted; therefore, approximately 80 percent of the children were eligible to participate.

Of these eligible children, 278 enrolled, 194 from the 17-hydroxyprogesterone arm and 84 from the vehicle arm.

Some demographic information for the children in the follow-up study are listed in this slide.

The mean gestational age of the children who participated in the follow-up of each treatment arm was one week greater than that in the principal study.

As such, the follow-up children may represent a slightly lower risk subset of the total group of children from the principal study.

The mean age of the children in the follow-up study at the time of evaluation was 47.2 months from the children from the 17-hydroxyprogesterone arm, and 48 months in children from the vehicle arm.

As stated previously, the primary objective of the follow-up study was to determine if there were differences in achievement of developmental milestones between children whose mothers received 17-hydroxyprogesterone, and those whose mothers received vehicle, in the principal study, as measured by the Ages and Stages Questionnaire, otherwise known as the ASQ.

This primary endpoint of the follow-up study measured the proportion of children from each treatment arm who fell below a specified cutoff, at least one of the five developmental areas listed -- communications, gross motor, fine motor, problem solving, or personal/social.

A positive screen was defined as a score which was two standard deviations below the mean in any of these five areas.

The secondary objective of the study was to determine if differences existed between children whose mothers received 17-hydroxyprogesterone and those whose mothers received vehicle in the principal study in any of the following factors:

activity motor control, vision/hearing, height/weight, head circumference, gender specific play, or diagnosis by a physician.

These children also received a physical exam.

The results of the ASQ, the primary endpoint assessing developmental milestones, will be shown on the next two slides.

This slide lists the number of children whose ASQ scores were screened positive or two standard deviations below the mean.

The proportion of children below the cutoff in each developmental domain was similar for each treatment arm.

The area with the highest percentage of children with low scores was fine motor skills with approximately one in five children scoring below the cutoff.

Approximately one in ten children had scores below the cutoff in communication or problem solving.

Few children had low scores for gross motor, or personal social skills.

Overall, approximately 28 percent of children from each treatment arm, shown by the numbers in yellow at the bottom of the slide, scored below the cutoff in at least one domain.

The absence of an apparent difference between the treatment arms should be interpreted with caution because the number of children in this study is relatively small.

A second integrated evaluation concerned identification of the true positives among those children identified as potentially at risk for developmental delay based on their ASQ scores.

As stated previously, the purpose of the ASQ was to identify children who may require further evaluation by a physician.

Those children with at least one score below cutoff and who had a parental report of a diagnosis of developmental delay, made independently by a physician, were reviewed in more detail.

13, or 6.7 percent, of the children from the 17-hydroxyprogesterone arm, and 8, or 9.8 percent, of the children from the vehicle arm had an ASQ

score below cutoff in at least one developmental area and a reported diagnosis of developmental delay.

Of the 21 children, total, meeting both criteria, the most common ASQ domains falling below the cutoff were: Fine motor and communication for the 17-hydroxyprogesterone exposed children, and communication and problem-solving for the vehicle exposed children.

The results of the follow-up study revealed no substantial difference in the outcome of the children exposed to 17-hydroxyprogesterone compared to vehicle.

To summarize, the applicant is seeking approval for 17- alpha-hydroxyprogesterone caproate based on findings from a single clinical trial and a surrogate endpoint for infant mortality and morbidity, pre-term birth less than 37 weeks gestation.

We are concerned that these findings may not be applicable to other populations and that the pre-term birthrate in the vehicle arm is

considerably higher than that reported in another large Maternal Fetal Medicine Network study.

We are also concerned that there is a potential safety signal of increased fetal wastage in the 17-hydroxyprogesterone arm.

We are asking the members of the Advisory Committee to consider these issues during your deliberations later today.

Thank you.

(Applause.)

DR. DAVIDSON: I'm sorry. This will cover both the sponsor and the agency presentations.

I think, in fairness, I should start where we left off this morning with our incomplete list of questions.

Dr. Liu.

DR. LIU: I wanted to ask about the first study that was stopped because of the medication.

One was, what was the problem with the medication in terms of the quality in terms of the manufacturer.

And, two, have you had the opportunity to

combine the results of the completed datasets from the first and the second study for the outcomes as opposed to just the followup?

DR. HICKOK: Yes. Let me make sure that I have your questions correct.

In the response to the recall of the study drug, as we mentioned before, in the 001 Study, there was a Consent Decree cited; "Significant GMP," Good Manufacturing Practice, you know, violations, and that information is -- that is the only information that we have in the public domain.

So FDA, at that point, and the manufacture, recalled the study drug in the 001 trial.

And we don't have any other information other than that.

NICHD, as I stated, following that, decided that since there had been a recall of the manufacturer, and 17-p was no longer available at that point, basically, to initiate a new study.=

And, at that point, they also found a different manufacturer.

In terms of your second study about, you know,

did the sponsor go ahead and give information and integrate the data, even though the 001 Study was not complete, yes, we did go ahead and do that.

And I might remark, though, that it is percentage in the 001 Study to look at the percentage of women who actually went through the whole study; in other words, had an opportunity for a full course of drugs, and that was, between the two groups, only approximately 55 percent.

So for the purpose of efficacy, we chose to present the data from the 002 Study.

If I can present the results to you, though, of, you know, integrating these two studies, which we did for the purpose of efficacy, you will see the following findings here.

For pre-term birth less then 37 weeks of gestation in the integrated data, again, 17-p, 404 versus 209 in the placebo group, we saw the following pre-term birth rates: 38.1 percent versus 49.8 percent.

And, again, this "P" value was significant at the .0052 level.

For birth less than 35 weeks, the difference was 22 percent versus 30.6 percent, again, a "P" value of .02. Birth less than 32 weeks, these differences, with a "P" value of .003067.

And, again, for the primary outcome of birth less than 37 weeks, as we described previously, we did adjust that by logistic regression for the imbalance in the prior pre-term birthrate.

So I guess I would say, in conclusion -- I'm sorry, I'm looking at you over a monitor here.

In conclusion, now, even though we didn't feel that it was completely correct to integrate these two studies for the purpose of efficacy because the 001 Study received less than 60 percent full opportunity to get the full trial drug, nonetheless, we see that, integrating these results, we still see statistically significant endpoints for the primary endpoint of less than 37, but also less than 35, and less than 32.

DR. DAVIDSON: Dr. Simhan.

DR. Simhan: This is a question for Dr. Hickok.

Your intent or proposal is that the trial

inclusion and exclusion criteria should apply to clinical use; specifically, the inclusion criteria that I'm speaking of is the history of prior spontaneous pre-term birth of a singleton pregnancy.

And the two exclusion criteria in 002 that I'm asking about are hypertension requiring treatment, and seizure disorder.

DR. HICKOK: Yes, we do, Dr. Simhan. Thank you.

We do propose the same labeling indication because that is all we have information on, and it would be unfair to include people on those labeling that were not studied during the NICHD trial.

Specifically to your question about a single, you know, prior pre-term birth, we do not propose that Gestiva be labeled for anything other than that sole indication, because there are not clinical data supporting other indications.

DR. DAVIDSON: Dr. Harris.

DR. HARRIS: Yes. Thank you.

Could you address the stillbirths in the study, please?

You had, I think, eight in the treatment group

and only two in the placebo group.

Percentages weren't statistically significant, but it appeared to be a trend towards an increase in the treatment group. Part of that appeared to be infection.

Does that mean that bacterial vaginosis at the time of entry would be a contraindication, and/or should we look at stillbirth rates in this population a little closer before or as part of the Informed Consent for treatment?

DR. HICKOK: I'm sorry, Dr. Harris. At the very end -- if you would clarify the very end of your question about Informed?

DR. HARRIS: The question is, if there is a towards -- which appears to be a trend towards stillbirths, how do we address that as part of this overall approval process?

Do we need to look at more patients, or do we need to make that part of the drug labeling or Informed Consent? What is your --

DR. HICKOK: I see. Thank you for the -- yes. Thank your for the clarification.

Yes. Let me review the stillbirths with you from the 001 and 002 Studies.

And, again, to give you the overall integrated conclusions from the 17-p and placebo groups, there were seven stillbirths that occurred in the 17-p group, for a frequency of 1.7 percent, and four in the placebo group, for a frequency of 1.9 percent.

Six of these occurred antepartum, and one intrapartum in the 17-p group. Two in the placebo group antepartum and two intrapartum.

And, again, remember, when you compare across columns for raw numbers here, there is a 2-to-1 ratio of 17-p versus placebo patients.

You saw the analysis that I previously presented to you about stillbirths, and we actually took the -- or about miscarriages. I'm sorry, I misspoke.

We took the same approach with stillbirths, in that we know that stillbirth risk varies across populations. There are high-risk and low-risk groups for stillbirth, as described in a couple of very good, large recent surveys.

So we took the approach, and we looked at other information from clinical studies, both Network studies and from the literature, and have summarized this information for you on this slide.

And I want to remark, first, that four of these studies that I'm describing are actually randomized trials of 17-p versus placebo.

And these were the studies by John Hauth that I described to you previously, that used active military duty as a criteria for randomization.

And then a second study, the Johnson study, that we are all aware of from 1975. That's very well known.

Then I've included the 17-p study here with the data that I previously have shown to you.

And then one other study that's received a fair amount of attention because it is a recent study, and this is a study by Carrodo in Italy, that randomized women with 17-hpc versus placebo following a mid-trimester amniocentesis.

So, again, you know, the outcomes for pre-term birth are not presented, but, specifically, these

investigators examined that interval following the amniocentesis to see if there was any -- you know, any risk or any benefit from 17-hpc.

But going back to other Network, studies, again, one of the studies that has been performed by the Network that we feel has extremely valuable information is the Factor Five Leiden study, which, again, was an observational study.

Women were enrolled very early in the Factor Five Leiden study, you know, on average of 12 weeks or so.

So they were followed longitudinally throughout pregnancy, and there is good opportunity of, you know, getting very valid data on stillbirths.

And, in addition, the Factor Five Leiden study, again, as a Network study, is likely to comprise patients who are quite similar to other Network studies, like the 17-p study.

So for that reason, we feel that these numbers are quite good.

So when you look across the different columns

here, we see the Factor Five Leiden study.

We see that in the three randomized studies of 17-p versus placebo, we have 3.8 percent versus 1.3 percent for stillbirths in the Hauth Study.

We have 4.5 percent versus zero percent in the Johnson Study; 1.1 percent versus 0.6 percent in Corrodo; 1.9 percent versus 1.7 percent.

And our summary conclusions on these are that there is really no apparent association that we can determine from all the available data that we have collected that we feel are valid comparison groups.

So there is no association between 17-p exposure and the risk of stillbirth based on these numbers.

Did you wish for me to go further into the questions about BV and occurrence of bacterial vaginosis during pregnancy?

DR. HARRIS: Not necessarily. I should clarify.

The question I had was really about the antepartum versus the intrapartum. Presumably, unless there is a catastrophe, most intrapartum stillbirths should be preventable.

But it is the unmonitored, supposedly low- risk antepartum stillbirth that I was raising the concern about.

And since you mentioned the thrombophilia area, which is associated with an increase in stillbirths, it raises even more questions about selection criteria for the treatment with progesterone.

DR. DAVIDSON: Dr. Merritt.

DR. MERRITT: I would like to go back to the presentation of the studies on animal data and ask again about the teratogenic effects in two populations.

In the rodent population, as I read the slide, it appeared that the number of animals studied were between 8 and 15 in each study.

When the primate data was presented, I didn't see.

Anc could you please clarify those study numbers for us?

DR. HICKOK: Dr. Singh, will you review these studies again for us, please?

DR. SINGH: I am going to have to tell you that,

from my memory, I believe, it was three. An N of 3 for the monkey studies.

But I will have to -- in fact, at lunch, I can verify that. I have the actual references and everything with me.

But -- so for the two -- for the Cynomolgus monkey study -- if you want to bring that slide back up -- and the Rhesus monkey study, which is actually one and the same -- we want the next slide, please.

Okay. So this slide actually represents two different studies.

The Hendricks, et al, paper that was published in 1987 is the one that contains the data from both the Rhesus monkeys and the Cynomolgus monkeys.

And that is the study in which I believe there was an N of 3.

And, I'm sorry, I just need to pull that reference, and I will confirm that with you later on.

So, and then in the second studies, well, I have that reference, actually, in the Boardroom, and, again, I can make that available to you.

If there's any follow-up question for now on content?

DR. MERRITT: Could you go back to the rodent slide, please?

DR. SINGH: That's one slide back.

So you're correct. The C-57 Black Six Mice study. In that study, the N was 8 per group.

And in the Swiss Webster Mulhouse study, that the N was between 11 and 15 per group.

Again, you will notice that the route of exposure is different.

There are sub-dermal pellets or subcutaneous injections, so this is different than the intramuscular route. So there is a bit of extrapolation there.

DR. MERRITT: Thank you for that clarification.

I have one other question, which is why was castor oil included in the vehicle as opposed to some other compound?

DR. HICKOK: Yes. Castor oil has traditionally been included in a vehicle as a depot injection to, again, prolong the duration of action

at the 17-hpc.

If given orally, it is rapidly degraded and not bio-available.

DR. DAVIDSON: Dr. Lewis.

DR. LEWIS: Yes. I also was wondering a little bit about the castor oil.

Is Delalutin also in a castor oil? That's one.

And, secondly, it is bothersome that there is such a high background rate of pre-term births in the 002 Study.

And I know that if you compare it to the other Maternal Fetal Medicine Network Unit study, they had a much lower rate.

Were the same centers involved?

And what is the speculation on why the difference is so great?

Were the time periods overlapping at all?

You know, it's just -- that is bothersome.

DR. HICKOK: Thank you, Dr. Lewis.

Let me address each one of your questions separately, as I can.

And the first one I'll go to is, you had a

question about Delalutin and the formulation. And let me just show you some data on the comparison between the two.

Here, you see the Adeza-proposed product, or Gestiva. You see the studies 17-p 002, and, here, Delalutin.

And you see, again, the quantity of 17-hpc and the concentrations of benzyl alcohol, benzyl benzoate, and benzyl and castor oil are all identical between the three.

For your second question, I believe you're getting at the question of the pre-term birthrate and the placebo that Dr. Wesley raised.

And I'd like to invite Dr. Anita Dos, our bio-statistician, to address the issue of the pre-term birthrate in the placebo group.

DR. DAS: There are a lot of reasons why the pre-term delivery rate in HUAM which is the Home Uterine Activity Monitoring study, and the Study 002 could be different.

The most quantifiable reason is that Study 002 enrolled the population at higher than the HUAM

study.

And this is evidenced by looking at the number of previous pre-term deliveries in the 002 Study.

In the 002 Study, there was 32 percent that had greater than one previous pre-term delivery, and in the HUAM study, there were 22 percent of women.

The gestational age at the worst previous pre-term delivery was also slightly lower, at 29.7 weeks versus 30.2 weeks.

But, also importantly, the gestational age of the qualifying delivery in Study 002 was early, at 30.8 weeks, showing that this is a higher risk population.

There is other non-quantifiable reasons why these two studies might differ.

One would be the temporal reason in that Study 002 was completed in 2002. The HUAM study was completed in 1996.

And the MFMU Network was slightly different, with 19 participating centers in 002, and 11 participating centers in the HUAM study.

But, also, very important is the study design.

The HUAM study was not a randomized trial, it was an observational study.

Study 002 is a randomized trial with very intensive intervention. An injection once a week.

And we know from anecdotes that the women who participated in this trial were extremely motivated.

One: Because of their prior pre-term history and their adverse obstetrical history.

So, again, one of the non-quantifiable differences, truly, is an observational study versus a randomized trial.

I'd also like to have Dr. Savitz come and speak a bit to this point.

DR. HICKOK: And Dr. Savitz, I might add, is a reproductive epidemiologist.

DR. SAVITZ: Thank you.

David Savitz, Mount Sinai School of Medicine.

I can just maybe comment and just add to that that the -- sort of the art of predicting the baseline rates in randomized trials is a challenging one for those who have engaged in trials, and you use the -- of course, the best

historical data you have the best estimates.

But, as Dr. Das explained, the constitution of the patient groups will often differ and especially the willingness to participate, is a more subtle, but, I think, can be a very important influence on the baseline risk.

I don't think there has been so much a question about maybe whether the placebo group accurately reflects the baseline risk.

That is an issue of randomization, I think has been well taken care of.

But I think probably the concern is maybe with one of generalize-ability; that is, whether these results would apply to the full spectrum of women who meet the eligibility criteria of one or more prior pre-term births.

And, there, I think the data are clear in the various subgroup analyses, saying that all of the groups of varying background risk seem to share the same benefit.

That is, whether the groups are defined by number of prior pre-term births or other criteria --

bacterial vaginosis, and so on, as Dr. Hickok presented.

There's every reason to think that a different group with a different mix of those attributes would probably have a lower risk of pre-term birth. but there is a consistent pattern that they would be predicted to show the same benefit.

DR. DAVIDSON: Dr. Henderson.

DR. HENDERSON: I, too, am struck by the high background rate of pre-term delivery.

I wonder, from the literature, do you know what the background rate was in any of those publications, the ones that you used to cite in support of what the Maternal Fetal Network did?

DR. HICKOK: Yes. You know, it is quite remarkable about having spent, it seems like over a week looking, for this type of information.

You know, you probably go back to, you know, the quote from Robert Goldenberg that's widely cited, that there's a 20 to 40 percent risk of recurrent pre-term birth kind of period.

And we did look, and we can actually, you know,

show you some data from the 002 Study on the risk of recurrent pre-term birth, by the number of prior pre-term births, which is, you know, certainly a big risk.

And that goes up dramatically with each consecutive number of prior pre-term births.

In other words, those women that have one, versus those that have two, then those that have three. And it makes quite a -- it's quite remarkably higher as you move up.

A second variable that's been pointed out by the Network studies, and specifically Dr. Brian Mercer, has been a lower gestational age at the time of, you know, prior pre-term birth.

And I think, as Dr. Das pointed out to you in her presentation, that the average gestational age of the prior pre-term birth was about 30.9 weeks, which really is very low when you consider the data that Dr. Nageotte presented, that 75 percent of pre-term births occur between 34 and 37 weeks of gestation.

So, obviously, the women that entered into the

NICHD clinical study were at high risk. Very high risk, by virtue of number of prior pre-term births, and by the low gestational age at the qualifying pre-term birth.

DR. HENDERSON: One thing that strikes me, the age certainly is getting younger, gestational age.

But part of that is the multiple gestations, and that group was excluded from this trial.

So, in looking at the incidence of pre-term delivery is increasing, the age of gestation is decreasing, and part of that is the contribution of multiple gestations, and so that's not part of what we're looking at.

I'm just still struck by the high incidence of pre-term delivery in the placebo group.

And just other than just saying that the rate has increased over the baseline rate, in general, do you have any thoughts of how or what may be -- I mean, the vehicle or what -- the intervention?

And you would think that women who are in randomized clinical trials because of their history, as was stated, they are very motivated and they're

very cooperative, and they show up, and they don't know that they are getting placebo.

So it is very likely that they were really, really good patients, and they did what they were supposed to. So you would think that just the intervention would lower their risk.

So I just -- I can't get my hands around the 50-so odd percent of pre-term delivery.

DR. HICKOK: Yes. The women were certainly motivated, and they had, had, you know, a prior -- at least one prior very bad experience.

And I might even give you a little, you know, flavor for that at the study site by asking Ms. Gwendolyn Norman to talk a little bit about her relationship with patients. And she -- you know, she recruited them, she followed them.

Ms. Norman, would you step forward and just give us a little bit of flavor for the risk status of your patients and their motivations and compliance and all?

MS. NORMAN: Certainly. Gwendolyn Norman from Wayne State University.

In the original trial, the 002, we did find that the women were very willing to participate.

They had had, as you said, a very high risk of exposure. They had had a previous loss, were very compliant, and participating in coming weekly or, if they were on bed rest, for us to come out and do home visits for them.

DR. HICKOK: And I'd also like Dr. Paul Meis, the principal investigator of the study -- we're fortunate to have him here today -- to remark on this subject.

DR. MEIS: Paul Meis, Wake Forest University.

I can only say that, anecdotally, when I would recruit patients for this study, that when we explained the study to women, that they would receive weekly intramuscular injections from 16 to 20 weeks, all the way up to 36 weeks, and that there might be a chance that they're getting the placebo for no benefit, the women who had had a prior pre-term birth at, say, 35 weeks or so and the baby had done very well, they were not very interested in participating in this study.

But if the woman had had a pre-term birth at 28 or 29 weeks and the baby had stayed in the hospital for a long time and had problems, they were very interested in this study.

So I think there was a self-selection process involved.

DR. HICKOK: Thank you, Dr. Meis.

DR. DAVIDSON: Dr. Gillen.

DR. GILLEN: Thank you.

I hate to beat a dead horse here but, clearly, this is a sticking point in terms of the generalize-ability of what we're looking at.

So, it seems like one of the most plausible explanations that's been offered is that there's co-variate imbalances, effectively, with respect to risk factors for pre-term births between the 001 Study and the 002 Study.

And, I guess, I'm just wondering if the Committee can offer us any sorts of -- so, I mean, it begs the question, effectively, to say, which way are the imbalances going in terms of the general population or the target population that you're

going to be targeting here?

And so, is there any sort of literature or review that we have evidence for that says, you know, the target population currently today is more like the placebo group that was enrolled, or the group that was sampled for the 002 Study versus the 001 study, in order to help us make this distinction between the two?

DR. HICKOK: Yes. The answer off the top of my head, is, again, these were very motivated women that had had a bad experience.

And we would expect, you know, going forth, at least -- and, again, this is opinion on my side -- we would expect women who perceive themselves at higher risk to be more likely to engage in a course of treatment that involves something like weekly, you know, injections of a -- you know, of a drug and castor oil then we would people that, as Dr. Meis and Ms. Norman described, as those at 35 or 36 weeks that had had a child, but perhaps had a longer neonatal stay.

In terms of your -- I think you had almost a

second question about generalize-ability and all, too, and Dr. Savitz addressed that briefly.

But the stratified analysis that we presented to you, we sent to you during the core presentation, I think a very strong argument about the generalize-ability of the benefit of 17-p.

And, again, if we go to the first slide that I showed, this gets at the prior question, also, that was raised about risks by number of prior pre-term deliveries.

Again, we see in a population, with a lot of pre-term deliveries, those baseline risks in the placebo group can be very, very high if you have a large number of pre-term deliveries.

But on the issue of generalize-ability, whenever you start dividing groups into different strata and get consistent effects, it's a very strong argument about generalize-ability of the results.

And what we showed you here, previously, was the effect by number of prior pre-term births.

And then, secondly, we divided the population

into African-American versus non-African-American and saw the same general pattern as we did with the benefit of 17-p over placebo.

A third stratification was by bacterial vaginosis, which is a known risk factor, as Dr. Nageotte showed you.

And we would see the same kind of pattern about, you know, an increased risk in people with bacterial vaginosis in the placebo group, which you would expect.

But, similarly, a decrease that paralleled one and another between the "BV" and the no "BV" group.

So, because of those, you know, four ways that we stratified and all, it is a very strong argument that there is generalize-ability of those study results.

Dr. Savitz, would you have any further comments on this regarding our statistician's question here?

DR. SAVITZ: Very briefly.

I think that the best guess about what would happen if you reconstituted a different that had a lower risk distribution is to look at the data that

Dr. Hickok presented, and imagine a group with fewer multiple prior pre-term births or a lower rate of bacterial vaginosis.

Or, if you will, an average -- a more favorable risk factor profile.

The best evidence from the study says that group with a lower risk profile would share the same benefit as was observed in this population, given that the stratum specific results were so consistent.

So if you had a different mix of strata, if you will, you would still predict and anticipate the same kind of benefit.

DR. GILLEN: I certainly agree that there is consistency; I guess, that they're -- and true in terms of the point estimate, all pointing in the correct direction.

But, I mean, you know, there is variability there in terms of pre-gestational or pre-term births of less than one. You only have an 11 percent difference, going up to, you know, what we see as an average of 17 percent differences, and a maximum, I

think, 30 percent difference from what I saw on the previous slide.

So, you know, when we're weighing sort of efficacy versus safety, you know, the magnitude of a point estimate is very important; and so, therefore, what constitutes the population later on is going to be very important in terms of how that point estimate is going to fluctuate between, say, a 10 percent improvement and a 30 percent improvement, for example.

And so, I guess, that's my main point in terms of saying, you know, what is the population, or target population, truly going to look like.

And is it what we've seen in the past or what we see now with this 002 trial?

And I understand that is a very difficult question. I'm just trying to raise it and illustrate some of the things.

DR. SAVITZ: I think that, again, the data provide the basis for speculating about a different mix of the known risk factors.

But I think, as Dr. Meis mentioned, I think one

of the biggest -- you know, the issues is the self-selection into the study.

And, again, there is no reason to anticipate that a different mix of women with different motivation would experience a different consequence.

I think there is an issue, though, about the challenge of simply -- for this kind of a protocol, of having in a trial situation where there is that placebo arm, obviously, that people are aware of, to generate a group that really is fully representative of the clinical source population.

So there is that nature of generalize-ability always from randomized trials.

DR. DAVIDSON: Okay. Dr. Wenstrom.

DR, WENSTROM: A lot of concern was expressed about the five miscarriages in the 17-p group.

But a miscarriage was defined as a loss between 16 and 20 weeks. And I believe we were told that the average gestational age at the first dose was almost 19 weeks.

So do we even know that those five women got a

dose of 17-p or, if they did, if fetal viability was confirmed before they got that dose?

DR. HICKOK: So, Dr. Wenstrom, that has to do with combining the 001 data with the integrating. That's a very -- a very good question on your part.

And we actually did go back and look at, specifically, the number in Study 001 who completed treatment through 20 weeks of gestation.

In other words, we had a full course of treatment through 20 weeks gestation.

That number was 94.5 percent, so we felt very good about combining that with the data from 002, you know, and giving a bigger estimate and more stability of the numbers with, you know, again, almost 95 percent of the women in that 001 study, did complete treatment through 20 weeks.

DR. WENSTROM: Does this mean they had one dose at 19 weeks? The average -- wasn't that correct?

DR. HICKOK: It is possible that they had one dose.

But, again, the average gestational age at the time of randomization was almost identical between

the 001 and the 002 Study.

So there was a balance -- I'm sorry, between the 17-p and the placebo groups.

So there was a balance on, you know, when people entered the study and the average number of injections they received by 20 weeks.

DR. WENSTROM: But it's possible that some of those five women hadn't even received a dose; correct? They could have been randomized and counted as a loss?

DR. HICKOK: No. They were all randomized and given an injection of 17-p at the same day.

DR. WENSTROM: Okay.

DR. HICKOK: And that had -- again, that had to occur before 20 weeks, 6 days of gestation.

DR. DAVIDSON: I understand Dr. Kammerman from the FDA may have a question or comment on this.

DR. KAMMERMAN: Yes. One of the concerns I have regarding this discussion of safety, is that we're ignoring the time on study drug that you were getting at.

And if we looked at the distribution of

gestational age at randomization, 25 percent of the subjects were enrolled by 18 weeks, 75 percent by 20 weeks, and there were 25 percent that were enrolled during that last week.

So, right off, there is only 75 percent of the subjects that we're talking about.

And we need to look at the amount of time that they were actually on study drug.

For example, there was one subject who was lost follow up, and I think that person was counted as one day in the study.

So if we account for the exposure to the study drug, the percent of stillbirths -- I'm sorry, miscarriages is actually 3.5 percent. The percentage of deaths at 21 weeks is 6 percent versus just about zero for placebo.

And if the rate of death adds up, fetal death at 24 weeks, is 7 percent for placebo versus 3 percent -- I'm sorry, 7 percent for 17-p, and 3 percent for placebo, and then that's when you start seeing the curves come back together.

So if we do look at the amount of time that patients were on study drug, the rates become elevated when we use the proper denominator.

DR. HICKOK: Should I respond to that, Dr. Davidson, or are you going to take another question? Does that mean that I can respond?

DR. DAVIDSON: I think we will have to cut off for one hour for lunch to stay on schedule.

And, as usual, our list is longer than the time we have.

So we will pick up this afternoon with the discussion in terms of those that did not have an opportunity to raise a question.

Dr. Watkins may have some logistical comments about lunch.

DR. WATKINS: Just two housekeeping issues.

For the Committee, the hotel's restaurant has an area cordoned off so that you can quietly enjoy your lunch.

If so, if you will proceed to the restaurant, I would appreciate that.

For those members who have pre-registered to participate in the Open Public Hearing but have not yet checked in at the registration desk, please do so.

Thank you. And we'll see you after lunch.

(Whereupon, a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

MS. WATKINS: We'd like to call the first open public hearing speaker to the microphone. The first speaker is Senator Connie Lawson.

SENATOR LAWSON: Good afternoon. I am Indiana State Senator Connie Lawson and Vice Chair of Women in Government, a national 501(c)(3) non-profit bipartisan organization of women state legislators providing leadership opportunities, networking, expert forums, and educational resources to address and resolve complex public policy issues.

Women in Government leads the nation with a bold, courageous, and passionate vision that empowers and mobilizes all women legislators to effect sound policy. In the interest of disclosure, my trip today was paid for by Women in Government, and Women in Government does receive unrestricted educational grants from Adeza Biomedical.

As you all know, preterm birth is a burden to the American health care system. According to the March of Dimes, every week in the United States, nearly 9,600 babies are born preterm. In the course

of one year, over 12% of all live births are preterm.

Beyond the stress this causes for each family across our country, preterm birth has a lasting financial stress on our states and our nation, with over $18 billion spent nationally each year in hospital charges for babies born with low birth weight or prematurity.

I understand both these stresses on a personal level as a grandmother to two premature babies, one born at 29 weeks, one born at 32 weeks, and as a state legislator for 10 years.

We now understand the science and have the ability to prevent preterm birth. We also know that women who have previously had a premature baby are more likely to deliver prematurely in a subsequent pregnancy.

Progesterone treatments, such as 17P, have been shown in clinical studies, as we've all heard today, to have a positive effect on preventing preterm delivery. In the study conducted by the National Institute of Health, 17P was successful in reducing

preterm delivery by 34%.

Furthermore, the American College of Obstetricians and Gynecologists has recommended the use of progesterone in certain high-risk pregnancies, particularly for women who have previously had premature deliveries.

With available medicine and screening technologies, we can save lives, health care dollars, and undue stress on families in our nation. Women in Government has convened several educational forums on the issue of preterm birth, and many women state legislators across the country are addressing this important topic in women's health.

On behalf of my colleagues across the country, I urge the Advisory Committee to make recommendations to the Food and Drug Administration to improve the availability of preventative treatments for preterm delivery and to ensure access to life-saving technologies, such as 17P, for all women.

I thank you for the opportunity to speak to you

today, and I look forward to the important decisions you will make for the women of the United States, my family, and the people I represent.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our next open public hearing speaker is Barbara Dehn.

MS. DEHN: Good morning. I'm Barbara Dehn. I'm a women's health nurse practitioner, and previously, I was a pediatric ICU nurse at Stanford University Medical Center, so I know first-hand about the long-term issues of prematurity. Next slide.

When children are fortunate enough to survive their stay in the NICU, they go home to mom and dad and then if they become ill, they go back to peds or peds ICU, where I was a nurse. So I saw some of the things that they came in for. Next slide.

One of the things I saw a lot of was broncho-pulmonary dysplasia. This is also known as chronic lung disease. Those babies have very fragile lung tissue, so when they're mechanically ventilated, they can have scarring, and they can develop what's called chronic lung disease, almost like COPD in an

elderly person.

These children have a propensity to asthma, and small colds or flus that your child would brush off and be able to go to school with, these children can't, so they'd end up in the PICU with me and sometimes, they'd have to be ventilated. Next slide.

Another thing I saw was necrotizing enterocolitis. We called it NEC in the ICU. This is more common in children who are very low birth weight. If they did survive -- next slide -- this, because the mortality is very high, they often needed surgery, where a small portion of their very small intestine was removed.

So these children had chronic diarrhea and malabsorption syndrome. And so it was very interesting taking care of them in the PICU with chronic diarrhea, especially because they didn't grow very well. Next slide.

The other thing that was particularly difficult for me as a nurse was to see children who had developed intra-ventricular or peri-ventricular

hemorrhaging, and this is when their cerebral arteries or cerebral capillaries, excuse me, bleed and it would cause almost like a stroke in an older person.

Now, this is much higher risk in people who are delivered before 32 weeks, and small things that we did routinely in the ICU could trigger this. Just suctioning a child on a ventilator could trigger IVH. Next slide.

Now, the long-term consequences, I also saw. Children who had grade three or grade four IVH had much more serious sequelae and what I saw were children who came in for seizure disorders. So they seized and seized and seized and we couldn't get them under control.

Or their IVH made them more susceptible to hydrocephalus, and that's water on the brain. They needed shunting, and often times, they had to have shunt re-dos or their shunts became infected. And of course, we saw a lot of cerebral palsy, and those poor kids needed a lot of tendon-lengthening surgery. Next slide.

This is a partial list of risks factors. You know that. Next slide. You all know about the study by Meis, but what you may -- we should talk about is that using 17P decreases the rates of NEC, it decreases IVH, and it decreases the need for supplemental O2, or oxygen. Next slide. Next slide.

So what I want to talk about is the difference one week can make. So one extra week can make a huge difference in a child's life for their lifetime. Babies really do need to spend a lot of time in mommy's tummy. That's really where they develop best.

One extra week can mean the difference between reading at grade level and needing special education. It can mean the difference between wearing glasses and not wearing glasses. It can mean the differences between spitting up once in a while and having chronic reflux. It can mean the difference between running with your friends and being able to play soccer or having cerebral palsy, having spasticity, and needing tendon-lengthening

surgery.

Now, why don't we use more 17P? I work in the San Francisco Bay area. Stanford is nearby, we have Valley Medical Center. Both of those institutions have very different protocols for 17P. So it's difficult for me, as a women's health nurse practitioner, to initiate this for my patients, and that means limited access, and that also means under-treatment of women at risk. Next slide.

Because we don't have an FDA-approved formulation, it's not on every hospital formulary. It's not on my hospital formulary, and I work at El Camino Hospital in Mountain View, California in Silicone Valley. It's not covered by a lot of insurances. So for me, it makes it more difficult for me to do my job, and my job really is to help ensure healthy babies and healthy moms.

Because it has to be compounded, a lot of us are concerned about the quality assurance, and it is available through some pharmacies, but we're not really sure whether or not we should be using that for our patients. So I want to strongly -- next

slide -- I want to strongly encourage you to consider approving 17P, because I think it would help me do a better job of preventing the long-term consequences of prematurity.

I thank you for your time. In the interest of disclosure, a portion of my travel was paid for by Adeza Biomedical. Thank you.

DR. DAVIDSON: Thank you. Let me put this statement in the record. Fortunately, the first two speakers, I think, have complied with this. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making.

To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct

competitors. For example, the financial information may include the sponsor's payment for your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

MS. WATKINS: Thank you, sir. Our next presenter is Dr. Michael Paidas.

DR. PAIDAS: Dr. Davidson, members of the committee, ladies and gentlemen, thanks for the opportunity for being here. My name is Michael Paidas. I'm Associate Professor and Co-Director of the Yale Blood Center for Women and Children. I have paid for this on my own to attend here today. I've been part of the speakers bureau for the March of Dimes and Adeza Biomedical in the past. Next slide, please. Thanks.

So as you've all heard, preterm delivery is a

distressing problem, continues to have major issues for us for a number of different areas, and you've heard about the use of progesterone as a preventative strategy. Next slide, please.

You've heard a lot about the randomized trial completed by Dr. Meis and colleagues which showed that progesterone caproate IM weekly early on in pregnancy significantly reduced the risk of preterm delivery. Next slide. And you've also heard that it's improved the number of neonatal morbidities, as shown here.

You've also seen -- next slide. Thank you. You've also seen that a number of progestational agents have been used in the preterm delivery prevention, and in a recent med analysis that's shown here, you've seen -- and the conclusion was the use of these agents and particularly 17P has been shown to reduce the rate of preterm birth and low birth weight. Next slide.

Recently, also, ACOG has issued a committee opinion, also identifying that progesterone has greatly reduced the risk of preterm delivery, and

also stressed, I might add, that much more research is needed in these areas for patients with other high risk factors. Next slide. Thanks.

So I just want to highlight a bit about some of progesterone's actions and show you a little bit of the work that may have relevance to this topic. As you can see, progesterone has a number of actions. It relaxes the myometrial smooth muscle, it blocks the action of oxytocin, it inhibits the formation of gap junctions.

It also inhibits uterine prostaglandin production. It also inhibits T-lymphocyte mediated processes. It also seems to create a barrier to the entry of pathogens into the uterus, which is very important in terms of prevention of infection.

More recently, we've identified a number of issues of progesterone regarding the regulation of decidual cell homeostasis, those cells that come in direct contact with the placenta, and it seems to be that one of its effects is to block the effects of thrombin, which is involved in the clotting cascade. Next slide.

So we know that hemorrhage is one of the discrete pathogenic mechanisms involved in preterm delivery. In this cartoon here, you see the diagram where hemorrhage has occurred. When that does occur, there's an extravasation of a number of clotting factors, and that sets off the cascade to create thrombin.

Now, thrombin is one of the most potent uterine contractile agents that we're aware of. It's also involved in clot formation, certainly, but also, it's very much involved in the degradation of the extracellular matrix through the activation of a number of MMPs that you see on the right-hand side of the screen, which we think is important for involvement in preterm delivery. Next slide.

Recently now, we understand that thrombin induces decidual interleukin-8 expression, and interleukin-8 is very important in terms of recruiting neutrophils in the area. The panel on the right are two slides demonstrating a number of neutrophils in cases where you have abruption occurring, and in other cases on the top panel,

preterm delivery unassociated with abruption.

So now, we have a clear mechanism of thrombin being important in extracellular matrix degradation, and we've shown at least one compound of progesterone to reduce the risk of thrombin. So we have a potential mechanism of its effect. Next slide.

So as you know, there are a number of different candidates in various trials, but what we're talking about here today is women with a risk of preterm delivery based on a prior history. You've already heard already about the candidates for therapy. Next slide.

You've heard a lot about safety today, and a number of reviews have come out really attesting to the safety of progesterone. Next slide. So the main problem that we have right now is that we can't get doctors to access this drug, and having an entity that might be helpful for physicians nationwide to access the drug would be of great benefit.

So I would urge the committee to consider

seriously approving this drug for the treatment of -- prevention of preterm delivery. Thank you very much.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our next presenter is Nancy Green.

DR. GREEN: Thank you. My name is Nancy Green. I'm the Medical Director at the March of Dimes, and I'll be representing the foundation. First, in terms of the conflict of interest, I have no personal conflict to reveal. The March of Dimes has accepted donations from Adeza, and I can just say we've never discussed the topic of prevention of preterm birth or this application or progesterone with them.

So as many of you probably know, the mission of the March of Dimes is to prevent birth defects, prematurity, and infant mortality. On behalf of the over three million volunteers and 1,300 staff members of the March of Dimes nationwide, I will provide the foundation's perspective on this application for 17-alpha-hydroxyprogesterone caproate.

The March of Dimes offers the following recommendations to the committee based upon the promising results, and we've heard about it now several times already today from the Meis et al study through the (inaudible). It is our recommendation that: (1) the FDA approve the application to license 17- hydroxyprogesterone; (2) to direct that the FDA direct the product labeling to clearly be for the specific indications during pregnancy; i.e, prevention of recurrent preterm birth; and (3) that the FDA require a structured post-marketing evaluation of 17-hydroxyprogesterone by its proposed manufacturer.

Well, we've heard about the IOM (phonetic) report as well, so I won't mention that, but I would like to point out that based on the Meis et al study, the March of Dimes did an analysis based on 2002 birth data to estimate the impact of hydroxyprogesterone on prevention of recurrent preterm birth. This paper is published in Obstetrics and Gynecology in 2005, and we -- noting the historic rate of recurrent preterm birth

reported by Brian Mercer of 22%.

We looked at actually retrospective longitudinal data from two state health departments, maternal linkage, data sets that represent the ethnic distribution of the U.S., and actually, also found a recurrent preterm birth rate of 22%.

So all of those women who were eligible for progesterone as outlined by Meis et al, there would be 30,000 -- this is a estimate extrapolating from the Meis data -- approximately 30,000 recurrent singleton preterm births would occur, for which -- so those women would be eligible for progesterone. And if they had -- if all these women had received prenatal treatment with the drug, nearly 10,000 spontaneous preterm births would have been prevented; again, using 2002 data.

Widespread use of 17-hydroxyprogesterone for pregnant women has already been demonstrated amongst perinatal medicine specialists, maternal-fetal medicine specialists. A 2005 survey by Dr. Vince Bergella (phonetic), who's here in the audience, demonstrated that of those members surveyed -- or

responded, actually, to the survey -- that 67% -- that's two-thirds of the respondents already prescribed progesterone to their pregnant patients who are at risk of preterm birth. And that's data that was published as an abstract in 2005, and it's currently in press.

Interestingly, despite a lack of support of clinical data, one-third of the respondents -- these are maternal-fetal medicine specialists -- one-third of those who responded to the survey recommend progesterone for indications in addition to recurrent preterm birth, such things as effaced cervix and even tocolysis and other indications -- or other clinical situations.

Certainly, we've heard today that there's a paucity of published data around the safety issues on infants and children, although the datas appear to be favorable, but the March of Dimes continues to be cautious, of course, about the use of this drug, given the target population of pregnant women.

Certainly, the studies were not designed -- the clinical studies were not designed to provide

assurance of the drug's safety. Again, this is really why we encourage careful monitoring of the prescription use of 17-hydroxyprogesterone, including long-term data, as well as short-term potential manifestations, so we can best inform women and their prescribing providers around costs -- risks and benefits of 17P.

So therefore, given the common and serious problem of prematurity, as you've heard about, the unique property of 17- hydroxyprogesterone for reducing risk of preterm birth, the intended target user, pregnant women, and the documented widespread and broad prescription of the drug amongst perinatal specialists, the March of Dimes recommends that the FDA approve the licensing application for 17-hydroxyprogesterone.

If approved, that would mean that this drug would be available, if medically appropriate, to all pregnant women, including women who rely on Medicaid for health insurance and are risk of preterm birth. As you probably know, federal law prohibits Medicaid reimbursement unless the pharmaceutical or therapy

has received FDA approval and the manufacturer participates in a drug rebate agreement.

In fact, a number of states have already been working for Medicaid coverage for 17-hydroxyprogesterone. For example, the North Carolina legislature recently passed a bill in May of this year to provide funds from the Department of Health to cover the cost of purchasing the drug for low income women until "the medication becomes readily available through the Medicaid program."

MS. WATKINS: Ma'am? Your time is up.

DR. GREEN: Thank you very much.

DR. DAVIDSON: Thank you.

MS. WATKINS: Our next presenter is Joseph Hwang.

DR. HWANG: Good afternoon. My name is Joseph Hwang. And thank you for allowing me the opportunity to participate in this meeting. My name is Joseph Hwang. I'm a practicing maternal-fetal medicine specialist in Des Moines, Iowa. As a -- for disclosure, my trip was sponsored by Adeza Biomedical.